12/7/96

Visit to Russia on Collaborative Research on Dangerous Pathogens
(November 21-30, 1996)

PURPOSE OF THE VISIT

The NAS/IOM team had two tasks: (1) the identification of potential initial research projects at Russian institutions; these projects are to be supported using currently available funds provided by DOD of up to $500,000, which includes up to $85,000 for American collaborators and $15,000 for transfer fees; and (2) the establishment of arrangements for obtaining Russian inputs into a yet-to-be-developed Plan calling for long-term bilateral collaboration beginning in FY 1997. Appendix A identifies the team members. Appendix B identifies the American officials and Russian officials and specialists who met with the team.

BACKGROUND OF THE VISIT

In October, the NAS Committee Chairman and Vice-Chairman (Joshua Lederberg and John Steinbruner) sent jointly signed letters to Deputy Prime Minister Fortov and Deputy Minister of Defense Kokoshin advising them of the initiative and seeking their advice on how best to proceed. Fortov informally advised a Committee staff member to (a) consult promptly with the Ministry of Defense (MOD) concerning the activity, and (b) consider placing the initiative on the Gore-Chernomyrdin agenda. Either Fortov or his staff then designated Academician Lev Sandakhchiev, Director of the State Research Center of Virology and Biotechnology (*Vector*), to follow up on the initiative with the Committee. Kokoshin informally advised a Committee staff member through Russian intermediaries that he was not responsible for the topic and that the Committee should inform Chief of the General Staff Samsonov of the activity.

Several days before the arrival of the team in Moscow, the U.S. Defense Attache forwarded a letter to Samsonov from Committee Chairman Lederberg requesting that MOD receive the team. (Unfortunately, the letter had been delayed; and the Russian translation may have conveyed an erroneous impression that the Committee was focusing heavily on monitoring of Russian facilities.) On the eve of the team's arrival, MOD responded to the Embassy that such a meeting of the team at MOD was not necessary and that the Russian Academy of Sciences could invite specialists from MOD to participate in meetings on the topic if necessary.

As to Embassy assistance in arranging other visits, the Embassy requested the President's Commission on CW/BW Conventions to receive the team. The Commission declined. According to Russian colleagues, the Deputy Chairman would have received the team, but he was in Geneva at the intergovernmental BW review conference

being held at the same time. The Embassy requested a meeting for the Committee with the appropriate Deputy Minister of Health, and such a meeting was held. Also, the Embassy arranged meetings for the team with the Charge d'affaires, the Defense Attache, and the USAID health specialist.

Just prior to the team's arrival, the Committee Chairman sent letters to President Osipov and to Vice President Petrov of the Russian Academy of Sciences requesting that they receive the team, and a meeting with Petrov was arranged. Osipov was out of the city.

Several additional meetings were arranged by the staff of the Russian Academy of Sciences prior to the team's arrival, and other meetings were arranged by Academy staff and by the team members themselves after arrival.

As to the initial research projects, in October, the Committee had identified Vector, located in Koltsovo near Novosibirsk, and the State Research Center for Applied Microbiology in Obolensk in the Moscow district as the most appropriate sites for initial projects which could be rapidly launched. These centers have a history of working with dangerous pathogens in close collaboration with MOD institutions. Also, in recent years, they have developed a number of proposals for consideration by western collaborators, including some which have been given high marks in peer review competitions. Furthermore, the Director of Vector has participated in the arms control dialogues involving the National Academy of Sciences for several years. The Committee staff had alerted the Directors of the two institutes of the interest in their activities.

Also, the NAS had requested through the U.S. Department of State status as a "Partner" of the International Science and Technology Center (ISTC). ISTC provides a very convenient mechanism for contracting, financing, and other important administrative aspects of implementation of projects at Russian research institutions.

ESTABLISHING THE INITIAL RESEARCH PROJECTS

Criteria for Selection

During the visit, the team developed the following criteria for considering the merits of proposals for the initial projects:

- The project, or a discrete portion of the project, could be supported for a maximum of $200-225,000.
- The results of the research should have important public health implications for Russia, and possibly in other geographical areas as well.
- The proposal is technically sound and draws on a substantial body of science.

- The topic is appropriate for the research institution that will carry it out, with particular attention to the capabilities of the personnel and the facilities to support the project.
- There is a strong likelihood that discernible research results of significance could be achieved by September 1997, recognizing that they might only be interim results. This criterion means that only projects that have *already* been approved by the appropriate Russian government agencies would be eligible for funding as initial projects, since the Russian scientists stated that the time for Russian approval for new proposals is at least three months; and approval cannot be assured in advance.
- The project, if successful, would open up or would lead to an expansion of a significant area of research with important public health payoff. Adherence to this criteria would help distinguish the projects from ISTC-financed projects, which usually are not designed to lead to future research activities, but rather are intended to promote discrete short-term projects, thus allowing future resources to be used in other areas.
- There is the possibility that MOD scientists could be included within the project or within follow-on projects. Immediate involvement of these scientists is very desirable, but involvement at a later date as the research activity develops may be more realistic.

Vector (Koltsovo)

The Director, Deputy Director, and a senior scientist presented to the team five project proposals for consideration. The titles of the proposals are set forth in Appendix C. All of the proposals had been submitted to ISTC. Therefore, they had the necessary Russian agency approvals, and work could begin immediately.

The team noted that the proposal for development of an oral vaccine for Hepatitis B best fit the above criteria. The Vector scientists pointed out that the proposal had been submitted to ISTC two years ago, but it was not supported by the ISTC Financing Parties at that time due to the lack of preliminary data concerning aspects of the strains under consideration. In the absence of such data, there apparently were concerns as to the viability of the project. These data are now available and should resolve the concerns, according to the Vector scientists. They also pointed out that scientists from an MOD research institute in the town of Sergei Pasad just north of Moscow were interested in this proposal. If the project were supported, Vector would submit an amendment to the proposal to the appropriate Russian agencies in support of including MOD scientists in the activity. However, this approval process is expected to take at least three months and perhaps longer; thus the project would begin without MOD scientists.

The team gave special attention to the proposal supporting paleovirology investigations of influenza. However, the Vector scientists noted that this project would have to be a long-term

effort, since only one month each year was suitable for the expeditions to the north to collect human samples for analysis. There could be no assurance that appropriate samples could be obtained in July 1997 and if they were, that they would show indications of the virus of interest. The team noted that this project might be most appropriate for consideration with the framework of the long-term Plan to be developed by next September.

Having reviewed the candidate proposals, the team then considered whether a trip to Koltsovo was necessary. The team agreed that such a trip was important for several reasons. Firstly, members of the Committee who are experts in virology should visit the research facilities in Koltsovo to confirm the quality of staff and facilities that would support the various projects. Secondly, unanticipated problems with one or more of the proposals or new opportunities with other proposals might emerge. Thirdly, a visit to Vector will provide an opportunity to discuss approaches to identifying projects to be included in the longer term Plan. Given that Sandakhchiev is probably the most reliable interlocutor for supporting NAS activities in Russia currently and that he is knowledgeable about activities of other institutions as well, these preliminary discussions could cover ways for considering projects that might be conducted not only by Vector but by other institutions as well. Fifthly, the American specialists could begin a dialogue in support of expanded epidemiologic monitoring given their expertise and experience, both internationally and domestically, in this key domain.

Institute for Applied Microbiology (Obolensk)

The Institute for Applied Microbiology presented six proposals for consideration by the team. The titles of the proposals are set forth in Appendix D. However, only two of the proposals had the necessary government approvals. The others will not be considered until March by the State Committee on Science and Technology which is a key organization in the approval process.

After listening to presentations on the six proposals by the principal investigators of each of them, and taking into account the above criteria, the team gave special attention to the proposal to develop improved "molecular-biologic and immuno-chemical methods" for analysis of clinical strains of mycobacteria responsible for tuberculosis and mycobacteriosis. This proposal has been approved by the Russian agencies. An attractive aspect of this study is that it is a subpart of a not-yet-approved larger proposal to address other, highly dangerous pathogens (e.g. plague, anthrax, tularemia, brucellosis) as well. According to Russian scientists who participated in the discussions, if the more limited proposal were accepted, they could immediately seek approval for including other pathogens of interest to the Committee. If their amendment is accepted by the concerned Russian agencies, the original activity could then be broadened easily to include such pathogens.

The team decided that another visit to Obolensk prior to the Committee's selection of the most appropriate project would not be necessary.

As to conditions in Obolensk, the scientific staff is in a difficult economic position, although probably not as difficult as the financial plight at many other institutes. During the past several years the staff has dwindled from over 3000 to 1400. Since the institute is designated a State Research Center, it receives special funding from the State Committee for Science and Technology. Of considerable importance, it has eight projects funded by ISTC. Also, it has had NASA projects.

Mary Kay Cosmetics has established a significant operation at Obolensk, attracting a number of specialists with medical training. Also, there are a half dozen small enterprises with various types of medical-related products which have spun off from the Institute, and the US-Russia joint venture Mir is building a plant to produce generic pharmaceuticals (e.g. vitamins, anti-biotics) in a corner of the Institute's property.

ESTABLISHING NETWORKS FOR INPUTS INTO THE COMMITTEE'S PLAN

The MOD Inputs

High priority was given by the team to developing pathways for MOD inputs into the longer term Plan, given the refusal of MOD to arrange a meeting involving MOD specialists and the team, at least during this initial visit to Russia. Several organizations and individuals expressed interest in assisting in this regard.

- Both Vector and the Institute for Applied Microbiology have regular interactions with MOD specialists with whom they work on specific projects funded exclusively by Russian agencies.
- The representative of Biopreparat--the parent organization for Vector and the Institute for Applied Microbiology and which in Soviet times served as the interface between biological defense requirements and research programs in support of those requirements in many areas--indicated a readiness to assist in brokering contacts with MOD. He underscored the long-standing links between many of the eleven Biopreparat institutes and MOD.
- The ISTC is prepared to organize one or more workshops that are likely to include MOD scientists. ISTC has a track record in this regard having secured participation of twelve MOD scientists in an ISTC workshop last year, with the specialists from the MOD research institute in Kirov having presented two or three papers. (See Appendix E.)
- An important staff member of the President's Defense Council (Sergei Kortunov) expressed a willingness to encourage MOD scientists to participate in workshops in Moscow concerning the project upon our request for such assistance.
- An expert of the Duma Defense Committee (Natalia Kalinina) offered to help broker contacts with MOD scientists.

- A key official of the Ministry of Foreign Affairs (Sergei Kislyak) agreed to forward correspondence to senior officials of MOD who are in key positions in the BW-related field.

The team made no commitments as to how the Committee will proceed in the future. In each case, the team informed Russian colleagues that the Committee would be back in touch with them.

The U.S. Embassy strongly recommended using as many channels as possible to encourage MOD scientists to participate in the planning. The U.S. Charge recognized the political importance of the program and encouraged strong efforts to put it in place. The U.S. Defense Attache noted the financial plight of professionals throughout MOD. He thought that given its many other problems, MOD would give low priority to other technical justifications of the proposed collaborative program such as anti-terrorism and protecting the health of military personnel.

Both the Russian Ministry of Health and the Russian Academy of Sciences suggested that the team pursue its independent channels to reach Russian scientists of relevance to the project. Even though MOD had suggested that the Academy of Sciences could provide a venue for meetings with MOD personnel, the Academy did not mention this possibility.

The Gore-Chernomyrdin Agenda

Several Russian officials suggested that the program be put on the Gore-Chernomyrdin Commission agenda. They noted that endorsement at the highest level would help signal MOD scientists that the program was legitimate and important. At the same time, they pointed out that three committees of the Commission had interests--defense conversion, health, and science and technology.

In discussing among themselves the possibility of including the item on the Commission agenda, the team noted that placing it within the Defense Conversion Committee would encourage MOD as well as DOD to assume a responsibility for the implementation in both the short and long terms.

Interests of Other Agencies

Obviously, the Ministry of Health is a key player in any effort to promote public health. However, newly appointed Deputy Minister Onishchenko seemed more interested in obtaining immediate financial support for his institutes than discussions about long term plans. And he apparently has not embraced the Biopreparat complex of institutes--including Vector and the Institute for Applied Microbiology--as being important organizations of the Ministry of Health.

Specifically, Onishchenko complained that he had not been consulted as to the initial projects. As to providing inputs to

the long term plan, he seemed disinterested even though the Sanitary Epidemiological Service (*SanEpi*) which he still heads is the key organizations for epidemiologic monitoring within Russia. He did refer to his collaboration with CDC as important, however. Following the meeting, his staff called the American Embassy to say that the meeting should have been conducted at a lower level since there were no decisions for the Deputy Minister to make.

Petrov of the Russian Academy of Sciences received the group. However, he did not seem prepared to be helpful. He stated that while the inter-Academy agreement called for the Russian Academy to cooperate in activities such as the one being proposed, the Russian Academy had not made a decision whether it would play a "key role," possibly reflecting the fact that he had not had an opportunity to discuss the program with President Osipov. He raised concerns over the definition of "monitoring" which he apparently interpreted to mean monitoring of facilities. Also, he requested that the title of the project be changed to include "basic research" which was the purview of the Russian Academy of Sciences. He said he would await more details from NAS until taking any further steps. At the same time, he encouraged the team to develop its own channels to relevant agencies and institutions. The team indicated it would follow this advice, thus discouraging Petrov from seeking a role for the Russian Academy as a coordinator of Russian inputs into the Plan.

At the Academy of Medical Sciences, a group of apparently impoverished institute directors greeted the team. They were ready to cooperate in any field of interest, and they claimed considerable relevant expertise. The team agreed that they had much to offer. While not presenting specifics, the directors made it clear that they were in very difficult straights; and they had no funds for collaborative activities. Indeed, they were desperately searching for foreign funds.

The State Committee for Science and Technology welcomed the initiative, and they were pleased that the NAS would use the ISTC for which the State Committee had developed an appropriate review system. They considered the NAS selection of Vector and the Institute for Applied Microbiology as sites for the initial projects to be a validation of the State Committee's selection of these institutes as State Research Centers. They stated that they could be helpful in efforts of the NAS to bring institutes from many organizations into the consultation process although they did not mention MOD specifically.

It is also worth noting that during a team member's call at the Ministry of Foreign Affairs, a key Russian official (Kislyak) stated that "reciprocity" should be an important aspect of the program, specifically including exchanges of working scientists between biological defense facilities of the Ministry of Defense in Russia nad the Department of Defense in the United States.

NEXT STEPS

The team considered the following next steps:

Launching the Initial Projects

After the visit of the second team to Vector in mid-December, the Committee should be asked to approve the recommendations for the initial projects. The recommendation for the project at the Institute for Applied Microbiology would be based on the visit to Obolensk as discussed above, and the recommendation for the project at Vector on the basis of the preliminary screening by the first team in Moscow and the visit to Koltsovo by the second team.

Once the Committee agrees on the projects, the ISTC would be asked to take the necessary steps for signing the project agreements and for promptly launching the projects.

An important question that still remains is the identification of the American collaborators for each project.

Development of the Plan

One aspect of the Plan will presumably be a long-term research program based at a number of Russian institutions, and particularly those that have been involved in research on biological defense. As a step in developing this aspect of the Plan, a workshop should be held in February to obtain Russian reactions and inputs to a tentative research program outline prepared by NAS/IOM. Biopreparat/Vector could be asked to take the lead in organizing the workshop, with other organizations also invited to send specialists to the meeting. Outreach to MOD specialists would be highlighted in this activity.

One approach might be to prepare a straw-man "Call for Proposals" which could be issued if the second phase is implemented. This straw-man could provide the document for consideration at the workshop. In preparing such a Call for Proposals, all the critical issues, including selection criteria, must be addressed. Also, the Russians are very familiar with the Call for Proposals approach which has been used by a number of western organizations in Russia in recent years.

A second aspect is the system for responding to incidents involving pathogens--in Russia, the United States, and world-wide. This topic will involve a different cast of players given the bureaucratic dominance by SanEpi, with the MOD and Biopreparat institutions having played very minor roles to date. A possible approach is to work through ISTC in organizing a workshop in, say, June which brings together four organizations--MOD, Biopreparat, SanEpi, and Academy of Medical Sciences, along with representatives from corresponding U.S. organizations and, perhaps the World Health Organization--to begin to address

details as to how the operational system in Russia could be upgraded, including the role of supporting research institutions when they have the needed expertise. Related efforts of NAS/IOM concerning response mechanisms in the United States could provide useful inputs into such a workshop.

The third aspect of the Plan concerns the "regulation" of activities involving dangerous pathogens. It includes some of the activities being discussed at the Geneva BW Review Conference. Possible areas of interest include reciprocal inspection visits, registries of pathogens, and even licensing of activities. This aspect involves different Russian specialists than the scientific aspects and will require different mechanisms for obtaining Russian inputs into the Plan.

CONCLUSION

The team succeeded in identifying several projects that on a preliminary basis appear to be excellent candidates for support during the initial phase of the program. The final selection should be completed in January, with steps then taken through the ISTC to support implementation of the projects.

All relevant Russian government agencies and several Academies and other important institutions have been informed of the purpose of the overall program. They have been invited to participate in the development of the long-term Plan. The next step is to provide these organizations with straw-man documents which will enable them to provide inputs on the substance of future activities as well as on organizational aspects.

Successful outreach to MOD specialists and effective interactions with the Ministry of Health will be of special importance. Once the initial projects are in place and drafts of sections of the long-term Plan are available, there seems to be a reasonable likelihood that these organizations will become seriously interested in the program, at the policy as well as the research levels.

POST-VISIT FEEDBACK

Upon return to the United States, the Committee staff was informed by the Russian Academy of Sciences staff that (a) Petrov had become more enthusiastic about the proposal, and (b) Kokoshin had informally discussed the program with Fortov and had urged Fortov to actively support the program. The Russian staffer suggested that should the Committee decide to have a workshop in Moscow in February to obtain Russian inputs on the long-term Plan, the Russian Academy could make the necessary administrative arrangements while at the same time the NAS Committee would be free to use whatever channels it deemed appropriate in arranging the program agenda and extending invitations for Russian participants.

For additional comments, contact Glenn Schweitzer, tel 202-334-2644, fax 202-334-2614

Appendix A

Members of NAS/IOM Team
(Visit to Russia, November 21-30)

Members of NAS Committee

John Steinbruner, Brookings Institution, Vice Chairman of Committee
Alexis Shelokov, Salk Institute
Matthew Meselson, Harvard University

Staff Members

Christopher Howson, Institute of Medicine
Glenn Schweitzer, National Research Council

Appendix B

Participants in Meetings in Moscow and Obolensk

U.S. Embassy

John Tefft, Charge d'affaires
John Reppert, Defense Attache
Scott Towsley, CTR Officer
John Zimmerman, Science Counselor
Evelyn Putnam, Science Officer
Premilla Nored, Science Officer (Health)
Jane Stanley, USAID Health Officer
Elena Gurvich, USAID Environmental Health Specialist

President's Defense Council

Yevgeniy Velikhov, Member
Sergei Kortunov, Senior Staff

Ministry of Foreign Affairs

Sergei Kislyak, Chief of Department for Disarmament and Political/Military Affairs

Ministry of Health

First Deputy Minister Gennadiy G. Onishchenko
Viktor M. Lykov, Director, Division of International Scientific Cooperation
Anatoliy A. Monisov, Director of Department for Sanitary-Epidemiologic Surveillance

"Biopreparat"

Grigoriy Ya. Shcherbakov, Chief of Section for Science and Industry
Aleksandr F. Zaitsev, Chief of Section

Russian Academy of Sciences

Rem V. Petrov, Vice President
Sergei S. Markianov, Head of Foreign Relations Department
Yuri A. Osipiyan, Director of Institute of Solid State Physics and Chairman of CISAC Counterpart Group
Yevgeniy D. Sverdlov, Director, Institute of Molecular Genetics

Academy of Medical Sciences

Nikolai F. Izmerov, Chief of Department of Preventive Medicine
Dmitri K. Lvov, Director, Institute of Virology (Ivanovski)
Boris F. Semenov, Director, Institute of Vaccines and Serums (Mechnikov)
Sergei G. Drozdov, Director, Institute of Poliomylitis and Viral Encyphalitis (Chumakov)
G. A. Suvodov, Director, Institute of Occupational Medicine
Vladimir Orlov, Chief of Foreign Department
Ludmila Melnikova, Foreign Department

State Committee for Science and Technology

Yuri N. Mshensky, Head of Department for Life Sciences

Aleksei M. Korostelev, Department of Bilateral Scientific-Technological Cooperation
Yuri P. Fomichev, Economic Adviser

State Research Center "Vector"
Lev S. Sandakhchiev, Director
Sergei V. Netesov, Deputy Director
Dr. Marenkova, Senior Scientist

State Research Center for Applied Microbiology
Nikolai N. Urakov, Director
Aleksei V. Stepanov, Deputy Director
Irina Ye. Svyato, Deputy Director
Eduard A. Svetoch, Chief of Department
Igor G. Shemyakin, Chief of Department
Anatoliy N. Noskov, Chief of Department
Konstantin I Volkovoy, Senior Researcher
Aleksei N. Alekseev, Chief of Department
Ludmila I. Kavyzina, Chief of Department
Nikolay A. Staritsin, Researcher

Duma Committee on Defense
Natalya Kalinina, Expert

International Science and Technology Center
Oles Lomacky, Executive Director
Alain Gerard, Executive Director-designate
Yuri B. Kondratenkov, Senior Project Manager

Officials Who Were Contacted but Meetings Not Held

Deputy Prime Minister Valdimir Fortov
Deputy Defense Minister Andre Kokoshin
Chairman of Presidential Commission on BW/CW Conventions Syutkin and Vice Chairman Ignatiev
Chief, Directorate for Protection Against Biological Weapons General Yevstigneev

Appendix C

Projects Suggested by State Research Center for Virology and Biotechnology "Vector"

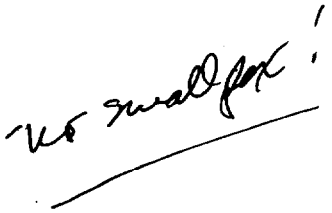
1. Creation of a live recombinant vaccine against Hepatitis-B for oral administration.

2. Sequencing of the genome of monkeypox virus pathogenic for humans.

3. Search for viable viruses and their genetic elements in neolithic remains of Gorny Altai and old cemeteries in the permafrost region of Russia.

4. Experimental studies of antiviral activity of glycyrrhyzic acid derivatives against Marburg, Ebola, and human immunodeficiency viruses.

5. Study of the genetic ancd serologic diversity of hantaviruses in the Asian part of Russia.



Appendix D

Projects Suggested by State Research Center for Applied Microbiology in Obolensk

1. Identification and investigation of a collection of causative agents of extremely dangerous infections (plague, anthrax, tularemia, mallei, tuberculosis, brucellosis) at the molecular and biological levels, obtained from various Russian regions.

2. Molecular-biological and immuno-chemical analysis of clinical strains of Tuberculosis and Mycobacteriosis.

3. Construction and investigation of molecular plague vaccine preparations which can provide early protection.

4. Development of bivalent live recombinant vaccines against brucellosis and anthrax.

5. Development of methods for specific immunotherapy of chronic melioidosis.

6. Cloning of *Pseudomonas pseudomallei* nucleotide sequences useful for the development of diagnostics.

Appendix E

MOD Presentations at ISTC Symposium
December 11-16, 1995

1. "Evaluation of Therapeutic Activity of Quinolone Group Preparations in Treatment of Severe Infections," N. T. Vasiliev, V. B. Kalinsky, B. A. Levchuk, S. M. Kuznetsov of the Research Institute of Microbiology of the Ministry of Defense of the Russian Federation, Kirov.

2. "Experimental Justification of Chemotherapeutical Methods for Plague Treatment at the Stage of Endotoxic Shock," N. T. Vasiliev, V. E. Romanov, V. A. Shabalin of the Research Institute of Microbiology of the Ministry of Defense of the Russian Federation, Kirov.

3. "Studies of the Development Problems of Specific Prevention and Treatment Means of Hemorrhagic Ebola Fever," A. A. Makhlai, V. V. Mikhailov, I. V. Borisevich, Center of Virology, Research Institute of Microbiology of the Ministry of Defense of the Russian Federation, Kirov.

MOD Participants from Kirov in ISTC Symposium

V. B. Kalinsky, I. D. Kravets, A. A. Makhlai (Director of Virology Center), N. V. Mikhailov, V. E. Romanov